PROFESSIONAL INFORMATION

DEXISUN should not be used outside an Intensive Care Unit setting or surgical operating theatres. There should be continuous monitoring of vital parameters.

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

DEXISUN Concentrated solution for intravenous infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of sterile solution contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine.

Contains sodium chloride (9,0 mg/ml)

For full list of excipients, see section 6.1

Sugar free.

3 PHARMACEUTICAL FORM

A clear, colourless solution, free from visible extraneous matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DEXISUN is an alpha-2 adrenoreceptor agonist sedative with analgesic properties indicated for:

- ***Intensive Care Unit (ICU) sedation***

Sedation of intubated and mechanically ventilated adult post-surgical patients during treatment in an intensive care setting.

- ***Monitored Anaesthesia Care (MAC) / Conscious sedation in a theatre or intensive care setting for:***
    - Minor surgical procedures under local anaesthesia
    - Fibreoptic intubation

Efficacy and safety has not been studied in children under 18 years of age.

4.2 Posology and method of administration

NOTE: DEXISUN should be administered only by healthcare professionals skilled in the management of patients in the intensive care setting. Continuous monitoring of vital signs, in particular blood pressure, heart rate and oxygen saturation is mandatory during infusion of DEXISUN.

In order to minimise undesirable pharmacologic side effects, bolus injection of DEXISUN should not be used.

Clinically significant events of bradycardia and sinus arrest have been associated with dexmedetomidine hydrochloride administration in young healthy volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of dexmedetomidine hydrochloride.

DEXISUN should be administered by continuous intravenous infusion not to exceed 24 hours. Fluid supplementation should be administered prior to and during administration of DEXISUN to ensure normovolaemia.

DEXISUN has been administered to patients requiring mechanical ventilation as well as to patients breathing spontaneously after extubation. There is no respiratory depression

associated with the administration of DEXISUN. Patients receiving DEXISUN have been observed to be arousable and alert when stimulated. This is an expected component of dexmedetomidine sedation and should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms. DEXISUN has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post extubation. It is not necessary to discontinue DEXISUN prior to extubation.

Posology

Adults:

ICU Sedation:

DEXISUN dosage should be individualised and titrated to the desired clinical effect.

Initiation:

For adult patients, it is recommended to initiate DEXISUN with a loading dose of 1,0 microgram/kg over ten minutes.

Maintenance of ICU Sedation:

Adult patients will generally require a maintenance infusion in the range of 0,2 to 0,7 micrograms/kg/h. The rate of the maintenance infusion can be adjusted in order to achieve the desired clinical effect. Dosages as low as 0,05 micrograms/kg/h have been used in clinical studies.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic or renal function and in patients over 65 years of age (see sections 4.3, 4.4 and 5.2).

Conscious Sedation:

Monitored anaesthesia care (MAC) with an adequate nerve block and awake fibreoptic intubation (AFI).

DEXISUN dosing should be individualised and titrated to the desired clinical effect.

Initiation:

For adult patients, DEXISUN is generally initiated with a loading infusion of 1 (one) mcg/kg over 10 minutes.

For patients over 65 years of age or those undergoing less invasive procedures such as ophthalmic surgery, a loading infusion of 0,5 mcg/kg over 10 minutes may be suitable.

Maintenance of Conscious Sedation:

MAC – Following the load, maintenance dosing of DEXISUN should generally be initiated at 0,6 mcg/kg/h and titrated to achieve desired clinical effect with doses ranging from 0,2 to 1 mcg/kg/h for all procedures. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

AFI – Following the load in awake fibreoptic intubation, a fixed maintenance dose of 0,7 mcg/kg/h should be used.

Special populations

Elderly:

Since the elderly are more sensitive to the effects of DEXISUN dosage reductions may need to be considered (see section 5.2).

Impaired Hepatic Function:

Dosage reductions may need to be considered for patients with hepatic impairment, as DEXISUN is metabolised primarily in the liver (see section 4.4 and 5.2).

Impaired Renal Function:

Since the majority of metabolites are excreted in the urine, dosage reductions may need to be considered for patients with renal impairment (see section 5.2).

Paediatric population

Safety and efficacy of DEXISUN has not been studied in children and adolescents and is therefore not recommended for patients under 18 years of age (see section 5.2).

Dosage Adjustment:

Due to possible pharmacodynamics interactions a reduction in dosage of DEXISUN or other concomitant anaesthetics, sedatives, hypnotics or opioids may be required when co-administered (see section 4.5).

Method of administration

For IV infusion only.

A controlled infusion device should be used to administer DEXISUN.

Parenteral products should be inspected visually for particulate matter and discolouration prior to administration.

Vials are intended for single patient use only.

For information on instructions for preparation or reconstitution see section 6.6.

DEXISUN must not be mixed with other medicinal products or diluents except those mentioned in section 6.6.

4.3 Contraindications

DEXISUN is contraindicated in:

- patients with known hypersensitivity to dexmedetomidine or to any other ingredient of DEXISUN listed in section 6.1.

- patients with sepsis
- unstable trauma patients
- hypovolaemic patients
- heart block
- uncontrolled cardiac failure
- imminent hepatic failure
- uncontrolled hypotension
- acute cerebrovascular conditions
- pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

DEXISUN should be administered only by healthcare professionals skilled in the management of patients in the intensive care setting and who have received complete training in the use of DEXISUN in the ICU setting.

Continuous electrocardiogram (ECG), blood pressure and oxygen saturation monitoring are mandatory during infusion of DEXISUN.

Safety and efficacy of DEXISUN in non-surgical intensive care patients have not been reported.

Clinical events of bradycardia and sinus arrest have been associated with DEXISUN administration in some young, healthy volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of DEXISUN. Bolus injections of DEXISUN should not be used, in order to minimise undesirable pharmacological side effects.

Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea (see section 4.8).

The time to recovery after the use of dexmedetomidine as in DEXISUN was reported to be approximately one hour. When used in an outpatient setting close monitoring should continue for at least one hour (or longer based on the patient condition), with medical supervision continued for at least one further hour to ensure the safety of the patient.

Caution should be exercised in patients with pre-existing severe bradycardia disorders (i.e. advanced heart block), or patients with pre-existing severe ventricular dysfunction (e.g. ejection fraction < 30 %) including congestive heart failure and cardiac failure in whom sympathetic tone is critical for maintaining haemodynamic balance (see section 4.3).

Hypotension, Bradycardia and Sinus arrest:

Decreased blood pressure and/or heart rate may occur with the administration of DEXISUN. Based on clinical experience with DEXISUN, if medical intervention is required, treatment may include decreasing or stopping the infusion of DEXISUN, increasing the rate of intravenous fluid administration, elevation of the lower extremities and use pressor agents. Because DEXISUN has the potential to augment bradycardia induced by vagal stimuli, medical practitioners should be prepared to intervene. The intravenous administration of anticholinergic agents should be considered to modify vagal tone. In clinical trials, atropine and glycopyrrolate were effective in the treatment of most episodes of DEXISUN-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

DEXISUN decreases sympathetic nervous activity and therefore, these effects may be expected to be most pronounced in patients with desensitised autonomic nervous system control (i.e. elderly, diabetes, chronic hypertension, severe cardiac disease).

Prevention of hypotension and bradycardia should take into consideration the haemodynamic stability of the patient and normovolaemia must be ensured prior to the administration of DEXISUN. Patients who are hypovolaemic may become hypotensive under DEXISUN therapy. Therefore, fluid supplementation should be administered prior to and during the administration of DEXISUN.

Additionally, in situations where the vasodilators or negative chronotropic agents are administered, co-administration of DEXISUN could have an additive pharmacodynamics effect and should be administered with caution and careful titration (see section 4.5).

Clinical events of bradycardia or hypotension may be potentiated when DEXISUN is used concurrently with propofol or midazolam. Therefore, consider a dose reduction of propofol or midazolam (see section 4.5).

Transient Hypertension:

Transient hypertension has been observed primarily during the loading infusion, associated with initial peripheral vasoconstrictive effects of DEXISUN and relatively higher plasma concentrations achieved during the loading infusion. If intervention is necessary, reduction of the loading infusion rate may be considered. Following the loading infusion, the central effects of DEXISUN dominate and the blood pressure usually decreases.

DEXISUN may cause reduced lacrimation. Lubrication of the patient's eyes may be considered when administering DEXISUN to avoid corneal dryness.

DEXISUN should not be given as a bolus dose and in the ICU a loading dose is not recommended. Users should therefore be ready to use an alternative sedative for acute control of agitation or during procedures, especially during the first few hours of treatment.

During procedural sedation a small bolus of another sedative may be used if a rapid increase in sedation level is required.

Some patients receiving dexmedetomidine as in DEXISUN have been reported to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

Dexmedetomidine as in DEXISUN normally does not cause deep sedation and patients may be easily roused. DEXISUN is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

DEXISUN should not be used as a general anaesthetic induction agent for intubation or to provide sedation during muscle relaxant use.

DEXISUN lacks the anticonvulsant action of some other sedatives and so will not suppress underlying seizure activity.

Care should be taken if combining DEXISUN with other substances with sedative or cardiovascular actions as additive effects may occur.

DEXISUN is not recommended for patient controlled sedation. Adequate data is not available.

When DEXISUN is used in an outpatient setting patients should normally be discharged into the care of a suitable third party. Patients should be advised to refrain from driving or other hazardous tasks and where possible to avoid the use of other agents that may sedate (e.g. benzodiazepines, opioids, alcohol) for a suitable period of time based on reported effects of dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient.

Patients with hepatic impairment

Care should be taken in severe hepatic impairment as excessive dosing may increase the risk of adverse reactions, over-sedation or prolonged effect as a result of reduced dexmedetomidine clearance.

Patients with neurological disorders

Experience of dexmedetomidine as in DEXISUN in severe neurological disorders such as head injury and after neurosurgery is limited and it should be used with caution here, especially if deep sedation is required. DEXISUN may reduce cerebral blood flow and intracranial pressure and this should be considered when selecting therapy.

Other

Alpha-2 agonists have less frequently been associated with withdrawal reactions when stopped abruptly after prolonged use. This possibility should be considered if the patient develops agitation and hypertension shortly after stopping DEXISUN.

DEXISUN may induce hyperthermia that may be resistant to traditional cooling methods. Dexmedetomidine treatment should be discontinued in the event of a sustained unexplained fever and is not recommended for use in malignant hyperthermia-sensitive patients.

Elderly:

The elderly are more prone to cardiovascular adverse events e.g. hypotension and bradycardia and the dose must be carefully titrated to obtain the desired effect. Close cardiovascular system (CVS) monitoring is required. Elderly patients (over 65 years) often require lower doses of DEXISUN.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P-450:

In vitro studies indicated that clinically relevant cytochrome P450 mediated interactions are unlikely.

Anaesthetics / Sedatives / Hypnotics / Opioids:

Co-administration of DEXISUN is likely to lead to an enhancement of effects with anaesthetics, sedatives, hypnotics, and opioids. Specific studies have confirmed these enhanced effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam.

No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to pharmacodynamic effects, when co-administered with DEXISUN, a reduction in dosage of these agents may be required.

Neuromuscular Blockers:

No clinically meaningful increases in the magnitude of neuromuscular blockade and no pharmacokinetic interactions were observed with DEXISUN and rocuronium administration.

The possibility of enhanced hypotensive and bradycardic effects should be considered in patients receiving other medicines causing these effects, for example beta blockers, although additional effects in an interaction study with esmolol were modest.

4.6 Fertility, pregnancy and lactation

The safety in pregnancy and lactation has not been established.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. The use of DEXISUN is not recommended in pregnancy.

Labour and delivery

The safety of DEXISUN in labour and delivery has not been studied and it is therefore not recommended for obstetrics, including caesarean section deliveries.

Breastfeeding

It is not known whether DEXISUN is excreted in human milk. The use of DEXISUN is not recommended in lactating women.

Fertility

In the reported rat fertility study, dexmedetomidine had no effect on male or female fertility. No human data on fertility are available.

4.7 Effects on ability to drive and use machines:

The patient should not drive or operate machinery or make legal decisions until 24 hours after recovery from surgical procedure in which DEXISUN was used.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions with DEXISUN are hypotension, hypertension, bradycardia, nausea, dry mouth and hypoxia (see section 4.4).

The following side effects have been reported during clinical trials and post-marketing surveillance and are listed by system organ class and frequencies indicated:

b. Tabulated list of adverse reactions

Table 1: Adverse Events with an Incidence > 2 % - ICU Sedation Population

System Organ class	**Frequency**	**Adverse event**
Blood and lymphatic system disorders	Frequent	Anaemia
Metabolism and nutrition disorders	Frequent Less frequent	Hypovolaemia, hyperglycaemia, hypocalcaemia, acidosis Hypoalbuminaemia
Psychiatric disorders	Frequent Less frequent	Agitation Hallucination

Cardiac disorders	Frequent Less frequent	Bradycardia, atrial fibrillation, tachycardia, sinus tachycardia, ventricular tachycardia, myocardial ischaemia or infarction Atrioventricular block, cardiac output decreased, cardiac arrest
Vascular disorders	Frequent	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Atelectasis, pleural effusion, hypoxia, pulmonary oedema, wheezing, respiratory depression Dyspnoea, apnoea
Gastrointestinal disorders	Frequent Less frequent	Nausea, dry mouth, vomiting Abdominal distension
Renal and urinary disorders	Less frequent	Polyuria
General disorders and administration site conditions	Frequent Less frequent	Pyrexia, hyperthermia, chills, oedema peripheral, withdrawal syndrome Drug ineffective, thirst
Investigations	Frequent	Urine output decreased
Injury, poisoning and procedural complications	Frequent	Post-procedural haemorrhage

Table 2 : Adverse Events with an Incidence > 2 % - Conscious Sedation Population

The majority of the adverse events were assessed as mild in severity. The most frequent adverse events were hypotension, bradycardia, and dry mouth. (See section 4.4)

System Organ class	**Frequency**	**Adverse event**
Cardiac disorders	Frequent	Bradycardia, tachycardia
Vascular disorders	Frequent	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent	Respiratory depression, hypoxia, bradypnoea
Gastrointestinal disorders	Frequent	Nausea, dry mouth

Post marketing adverse reactions:

System Organ class	**Frequency**	**Adverse event**
Infections and infestations	Less frequent	Infection, fungal infection, sepsis
Blood and the lymphatic system disorders	Less frequent	Anaemia, leukocytosis, coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia
Immune system disorders	Less frequent	Allergic reactions

Metabolism and nutrition disorders	Less frequent	Hyperglycaemia, hypoglycaemia, acidosis, lactic acidosis, respiratory acidosis, diabetes mellitus, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphate, increased Non-protein nitrogen (NPN), thirst
Psychiatric disorders	Less frequent	Agitation, anxiety, confusion, delirium, depression, hallucination, illusion, nervousness
Nervous system disorders	Less frequent	Convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder, syncope
Eye disorders	Less frequent	Diplopia, photopsia, abnormal vision

Cardiac disorders	Less frequent	Bradycardia, myocardial ischaemia, myocardial infarction, tachycardia Angina pectoris, dysrhythmia, atrial dysrhythmia, atrial fibrillation, AV block, bundle branch block, cardiac arrest, extrasystoles, heart block, hypoxia, supraventricular tachycardia, T-wave inversion, ventricular dysrhythmia, ventricular tachycardia
Vascular disorders	Less frequent	Hypotension, hypertension Haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation, circulatory failure, cyanosis, abnormal ECG, heart disorder, aggravated hypertension, pulmonary hypertension, postural hypotension, pulmonary hypertension

Respiratory, thoracic and mediastinal disorders	Less frequent	Adult respiratory distress syndrome, apnoea, bronchial obstruction, bronchospasm, coughing, dyspnoea, emphysema, haemoptysis, hypercapnia, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, pulmonary oedema, respiratory depression, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Gastrointestinal disorders	Less frequent	Abdominal pain, diarrhoea, eructation, mucosal ulceration, nausea, vomiting
Hepato-biliary disorders	Less frequent	Increased albumin to globulin (AG) ratio, increased gamma-glutamyl transpepsidase (GGT), abnormal hepatic function, hyperbilirubinaemia, increased aspartate transaminase (AST), increased alanine transaminase (ALT), jaundice.
Skin and subcutaneous tissue disorders	Less frequent	Rash erythematous, increased sweating

Musculoskeletal, connective tissue and disorders	Less frequent	Muscle weakness
Renal and urinary disorders	Less frequent	Increased blood urea, oliguria, haematuria, acute renal failure, abnormal renal function, urinary retention
General disorders and administration site conditions	Less frequent	Ascites, fever, hyperpyrexia, hypovolaemia, light anaesthesia, oedema, peripheral oedema, pain, withdrawal syndrome, rigors.

c. Description of selected adverse reactions

Withdrawal

ICU Sedation

Although not specifically studied, withdrawal symptoms similar to those reported for another alpha$_2$ adrenergic agent (clonidine) may result when DEXISUN is administered in excess of 24 hours and stopped abruptly.

These symptoms include nervousness, agitation and headache accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

Conscious Sedation

Withdrawal symptoms were not seen after discontinuation of short-term infusions of dexmedetomidine such as DEXISUN (< 6 hours).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reaction Reporting form', found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8.

4.9 Overdose

First-degree AV block and second-degree heart block may occur.

Bradycardia, with or without hypotension, and cardiac arrest may occur.

Because DEXISUN has the potential to augment bradycardia induced by vagal stimuli, medical practitioners should be prepared to intervene. In clinical trials, atropine and glycopyrrolate were effective in the treatment of DEXISUN-induced bradycardia (see section 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.9 Other analgesics. Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives, ATC code: N05CM18.

Dexmedetomidine is an alpha-2 adrenoreceptor agonist.

The sedative effects are mediated primarily by post-synaptic alpha-2 adrenoreceptors, which in turn act on inhibitory pertusses-toxin-sensitive G protein, thereby increasing conductance through potassium channels. The site of sedative effects of dexmedetomidine has been attributed to the locus ceruleus. The analgesic actions are mediated by a similar mechanism of action at the brain and spinal cord level.

Alpha-2 selectivity is demonstrated following low and medium doses given slowly. Alpha-2 and alpha-1 activity is seen following rapid administration. Dexmedetomidine has no affinity for beta adrenergic, muscarinic, dopaminergic, or serotonin receptors.

5.2 Pharmacokinetic properties

Following administration, dexmedetomidine exhibits the following pharmacokinetic characteristics: rapid distribution phase with a distribution half-life ($t_{1/2\alpha}$) of about 6 minutes; terminal elimination half-life ($t_{1/2}$) of approximately two hours; steady state volume of distribution (V_{ss}) of approximately 118 litres. Clearance has an estimated value of about 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female human subjects: the average binding was 94 % and constant across the different concentrations tested. Protein binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was statistically significantly decreased in subjects with hepatic impairment compared with healthy subjects.

Dexmedetomidine is unlikely to cause clinically significant changes in the plasma protein binding of fentanyl, ketorolac, theophylline, digoxin, lidocaine, phenytoin, warfarin, ibuprofen and propranolol.

Dexmedetomidine is eliminated almost exclusively by metabolism with 95 % of a radio-labelled dose being excreted in the urine and 4 % in the faeces. Approximately 34 % of the excreted metabolites are products of N-glucuronidation.

<u>Hepatic Impairment</u>

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values were reported to be lower than in healthy subjects. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were reported to be

74 %, 64 % and 53 % respectively, of those reported in the normal healthy subjects. Mean clearances for free drug were reported to be 59 %, 51 %, and 32 % respectively, of those reported in the normal healthy subjects.

Although dexmedetomidine is dosed to effect, it may be necessary to consider dose reduction depending on the degree of hepatic impairment (see section 4.2).

Renal Impairment

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{½}$, CL and V_{ss}) were not reported to be different in subjects with severe renal impairment (Cr CI: < 30 ml/min) compared with healthy subjects.

Gender

No difference in dexmedetomidine pharmacokinetics due to gender was reported.

Elderly

The pharmacokinetic profile of dexmedetomidine was not altered by age. The elderly are more sensitive to the effects of dexmedetomidine. In clinical trials, there was a higher incidence of bradycardia and hypotension in elderly patients (> 65 years of age).

Paediatric population

The pharmacokinetic profile of dexmedetomidine has not been studied in subjects less than 18 years.

5.3 Preclinical safety data

Reported non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

In the reported reproductive toxicity studies, dexmedetomidine had no effect on male or female fertility in the rat, and no teratogenic effects were reported in the rat or rabbit. In the rabbit study intravenous administration of the maximum dose, 96 µg/kg/day, produced exposures that are similar to those reported clinically. In the rat, subcutaneous administration

at the maximum dose, 200 µg/kg/day, caused an increase in embryofetal death and reduced the fetal body weight. These effects were associated with clear maternal toxicity. Reduced fetal body weight was noted also in the rat fertility study at dose 18 µg/kg/day and was accompanied with delayed ossification at dose 54 µg/kg/day. The reported exposure levels in the rat are below the clinical exposure range.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium chloride
- water for injections.

6.2 Incompatibilities

DEXISUN must not be mixed with other medicinal products or diluents except those mentioned in section 6.6.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 ^{o}C in the original container.

Do not refrigerate.

Once diluted, the diluted solution should be used immediately. If not used immediately, the diluted solution may be stored at 2 – 8 ^{o}C during the 24 hour “in use” period. Discard any unused diluted solution after 24 hours.

Keep out of reach of children.

6.5 Nature and contents of container

DEXISUN is packed in a 2 ml tubular, USP type 1 flint glass vial, with a 13 mm Teflon coated grey rubber stopper and a 13 mm pink aluminium flip-off seal, in a outer carton. Each carton contains 1 or 5 vials.

6.6 Special precautions for disposal and other handling

Preparation of Solution:

Strict aseptic technique must always be maintained during handling of DEXISUN infusion.

Preparation of infusion solutions is the same, whether for the loading dose or for the maintenance dose.

To prepare the infusion, withdraw 2 ml of DEXISUN concentrate and add to 48 ml of 0,9 % sodium chloride solution to total 50 ml. Shake gently to mix well.

After dilution, DEXISUN is intended for immediate use and should be discarded after 24 hours.

Administration with other fluids:

DEXISUN has been shown to be compatible when administered with the following intravenous fluids and medicines:

Lactated Ringers, 5 % Dextrose in Water, 0,9 % Sodium Chloride in Water, 20 % Mannitol, thiopental sodium, etomidate, vercuronium, bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine HCL, atropine sulphate, midazolam, morphine sulphate, fentanyl citrate and a plasma-substitute (i.e. Haemacel).

Compatability studies have shown potential for adsorption of DEXISUN to some types of natural rubber. Although DEXISUN is dosed to effect, it is advisable to use components with synthetic or coated natural rubber gaskets.

DEXISUN must not be mixed with other medicinal products or diluents except those mentioned above.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext 1

Roodepoort, 1724

South Africa

8 REGISTRATION NUMBER(S)

54/2.9/0218

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 June 2022

10 DATE OF REVISION OF THE TEXT

08 July 2022

Namibia NS3 22/2.9/0009